Leukemia

Introduction and Overview

This lesson is on the leukemias. There are many, but we want you to think of all leukemia as one of four types, permutations of acute/chronic and lymphoid/myeloid. Subtypes, variations, and details can confuse the picture. Keep this simple.

Acute leukemias are severe, rapid onset, and rapidly fatal. They are cancers of blasts, undifferentiated precursors. The patient presents with normal or reduced cell counts and lots of symptoms. Chronic leukemias are indolent and asymptomatic. They are cancers of mature differentiated cells. The patient will be asymptomatic but have a massively elevated white count.

Leukemias can arise from the myeloid progenitor and be myelogenous, or from the lymphoid precursors and be lymphocytic. The permutations are therefore acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL).

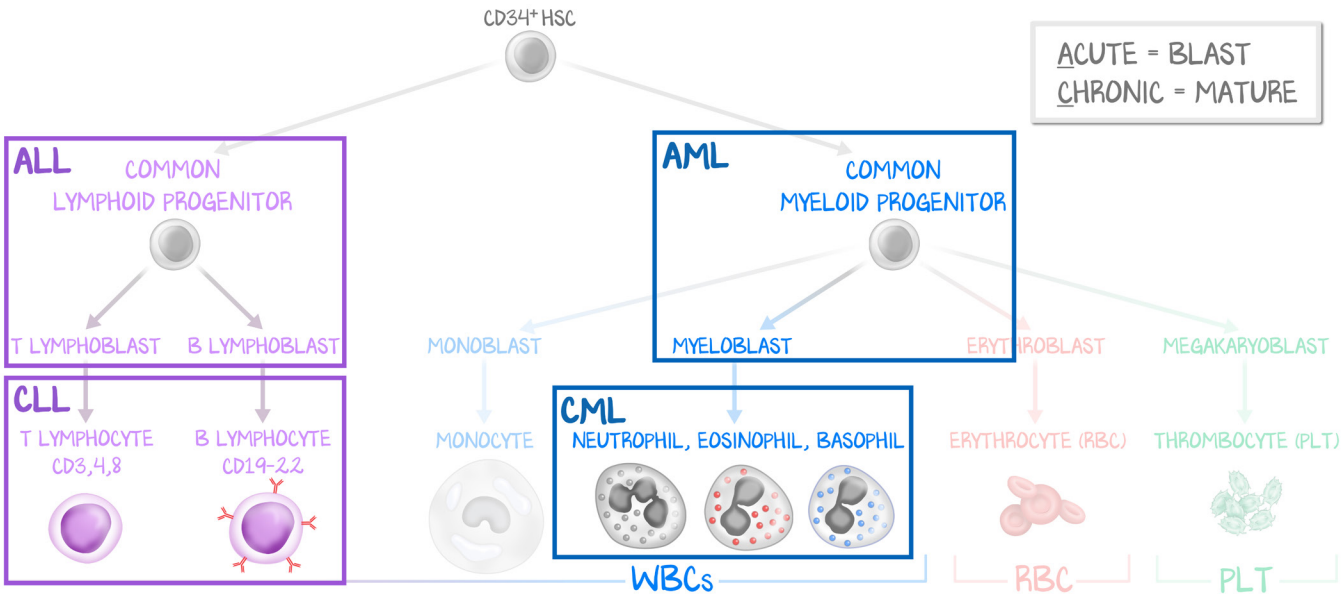


Figure 3.1: Leukemia Hematopoiesis
With a constrained look at hematopoiesis, focusing only on the cells that cause leukemia, hematopoiesis becomes much more simple. There are leukemias of the myeloid cell line and of the lymphoid cell line. Any leukemia can be dedifferentiated (acute, blasts) or well differentiated (chronic, mature cells).

Learn them as four diseases. ALL occurs in children, age 7. CML occurs in middle age, 47, and can turn into the really bad adult form of ALL or AML. AML happens because of CML, and since you get CML at 47, we say AML happens after, so age 67. CLL is the disease of old people, is rarely treated, and they die with it, not from it, so acquire it at age 87. These are not the actual median ages of incidence, but rather an advanced organizer to help you keep their presentations straight. Figure 3.2 helps orient you to age, acute vs. chronic, and progression.

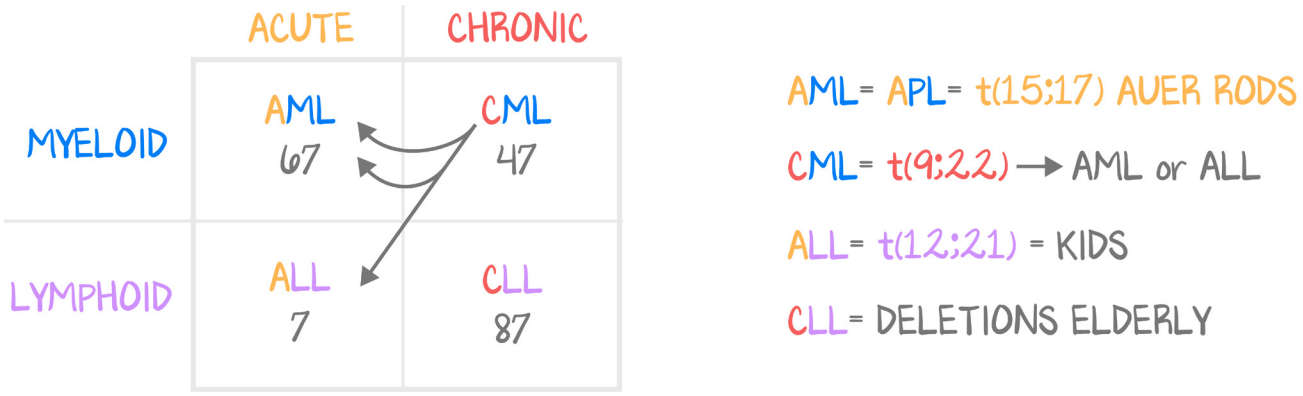


Figure 3.2: Leukemia Organizer
The two by two cell, superimposed with the "age of 7" helps keep the four leukemias straight. ALL is the cancer of kids, so 7; CLL is the cancer of the elderly, so 87; CML is 47 and because CML leads to AML, AML is 67. While there can be many mechanisms that arrive at malignancy, knowing the key translocations is critical for success on licensing exams.

After discussing the presentations of acute and chronic leukemia, we turn to the specific leukemias: AML, CML, ALL, and CLL.

Acute Leukemias

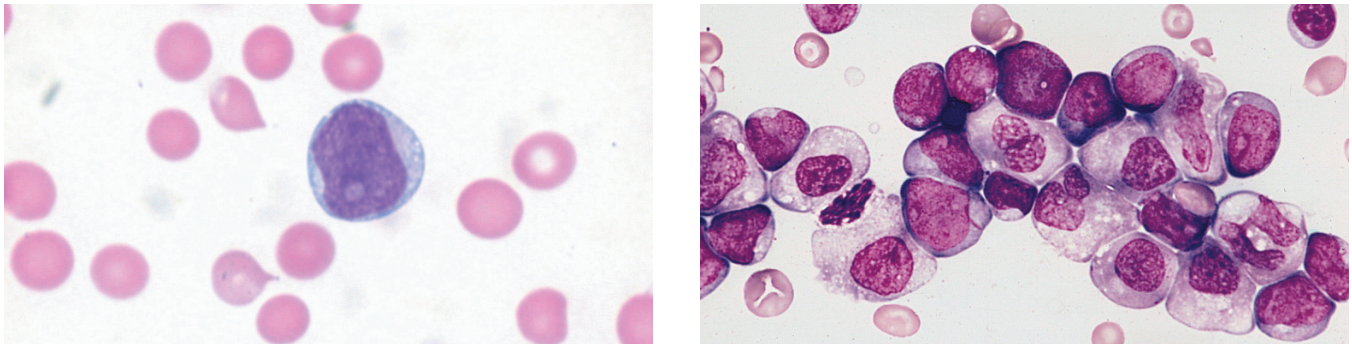
Acute leukemias, both lymphocytic and myelogenous, occur because of **impaired differentiation** (therefore remaining blasts) and **increased proliferation** (therefore making a lot of them). Acute leukemias are called acute because, relative to their chronic counterparts, acute leukemias present with high toxicity, are obvious, and are rapidly fatal if not treated. Acute leukemias cause a crowding out of the marrow, often presenting with **pancytopenia** (except for the malignant white cells, of course), and the symptoms are related to the loss of cell lines—**infection** (granulocytes), **bleeding** (platelets), and **anemia** (RBCs). There is often **bone pain** and **high fever** in acute leukemias.

Symptoms provoke a CBC that reveals a normal to slightly elevated white blood cell count. The differential will reveal a preponderance of one cell type (99% are one type of cell). A **blood smear** will show the presence of **blasts**. While blasts crowd the marrow, blasts usually do not crowd the blood. You should associate a high white count with chronic leukemia. The presence of blasts in the blood can mean only one thing—leukemia. Blasts are **huge** relative to the size of a red blood cell, are mostly nucleus, and have an obvious punched-out **nucleolus**. Blasts are early in the lineage. It is impossible to differentiate with the naked eye a B lymphoblast from a T lymphoblast from a myeloblast. The presence of more developed cells nearby may facilitate, but **flow cytometry** is used to determine which cells are in the greatest abundance. A diagnosis is made with a **bone marrow biopsy**.

T-CELL LYMPHOBLAST	B-CELL LYMPHOBLAST	MYELOBLAST	HSC
TdT	TdT	CD33	CD34
CD3	CD10		
CD4	CD19		
CD8	CD20		

Table 3.1: CD Markers

Leukemia is defined by an accumulation of blasts > 20% in the bone marrow. The presence of < 20% blasts in the marrow, but still blasts in the blood, is an indication of myelodysplastic syndrome.



(a) (b)

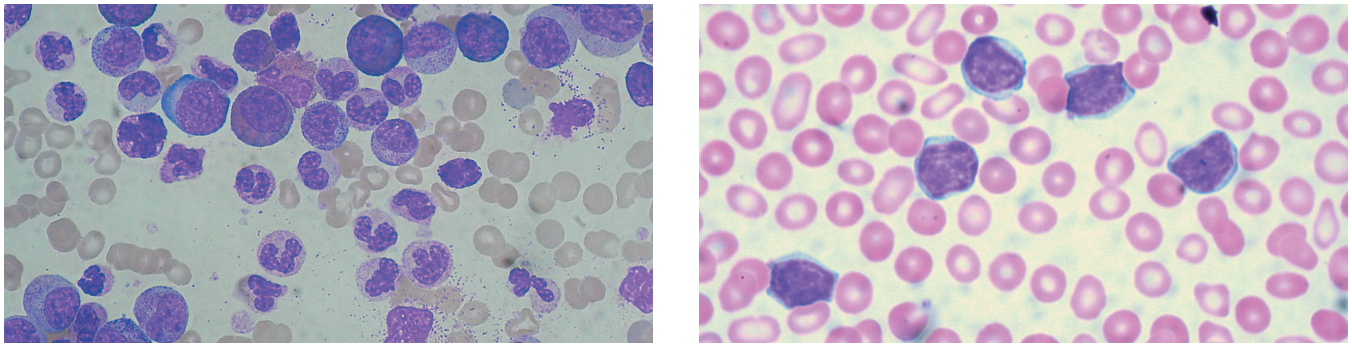
Figure 3.3: Acute Leukemia
(a) A blast in blood is identified by is enormous size, huge nucleus, prominent nucleolus and scant cytoplasm. (b) The blasts are more evident in bone marrow, some cells barely exhibiting any cytoplasm. All cells depicted are various degrees of immature. The more cytoplasm, the further along in development they are.

ALL is generally more obvious, occurs in younger patients, and is more symptomatic than AML. However, we want you seeing leukemias as either acute (pancytopenia, bleeding, infection, fever) or chronic (asymptomatic high white count). Then once you've decided acute or chronic, use the light microscope or flow cytometry to distinguish lymphoid from myeloid. Don't rely on patient symptoms or age alone.

Chronic Leukemia

The pathogeneses of the chronic leukemias are very different from one another. CML is from the BCR-ABL translocation; CLL is from a deletion. But they have a similar presentation. Chronic means mature; leukemia means in the blood. Mature differentiated malignant cells usually do what their nonmalignant versions do. Therefore, there are fewer symptoms. CML is more symptomatic than CLL, but both are far more indolent than their acute leukemia counterparts.

Chronic leukemias tend to have **insidious onset**, be **well-differentiated**, and have a **very high white count** but be asymptomatic. A WBC > 50,000 is indicative of a malignancy, though both CML and CLL can get above 100,000. Because chronic leukemias are differentiated, it is easy to separate CML (looks like neutrophils) from CLL (looks like lymphocytes). So the **blood smear** is sufficient to ballpark the diagnosis. Flow cytometry and bone marrow biopsy are performed to ensure the diagnosis before starting chemotherapy, though for the test you may be asked to make a diagnosis solely on a blood smear.



(a) (b)

Figure 3.4: Chronic Leukemias
(a) CML blood smear. The obviously different size and shapes of leukocytes (the big purple things) represent blasts in various stages of differentiation. (b) CLL blood smear does not look nearly as angry. The cells are mostly nucleus (looks like a lymphocyte) and is about the size of a red blood cell (looks like a lymphocyte).

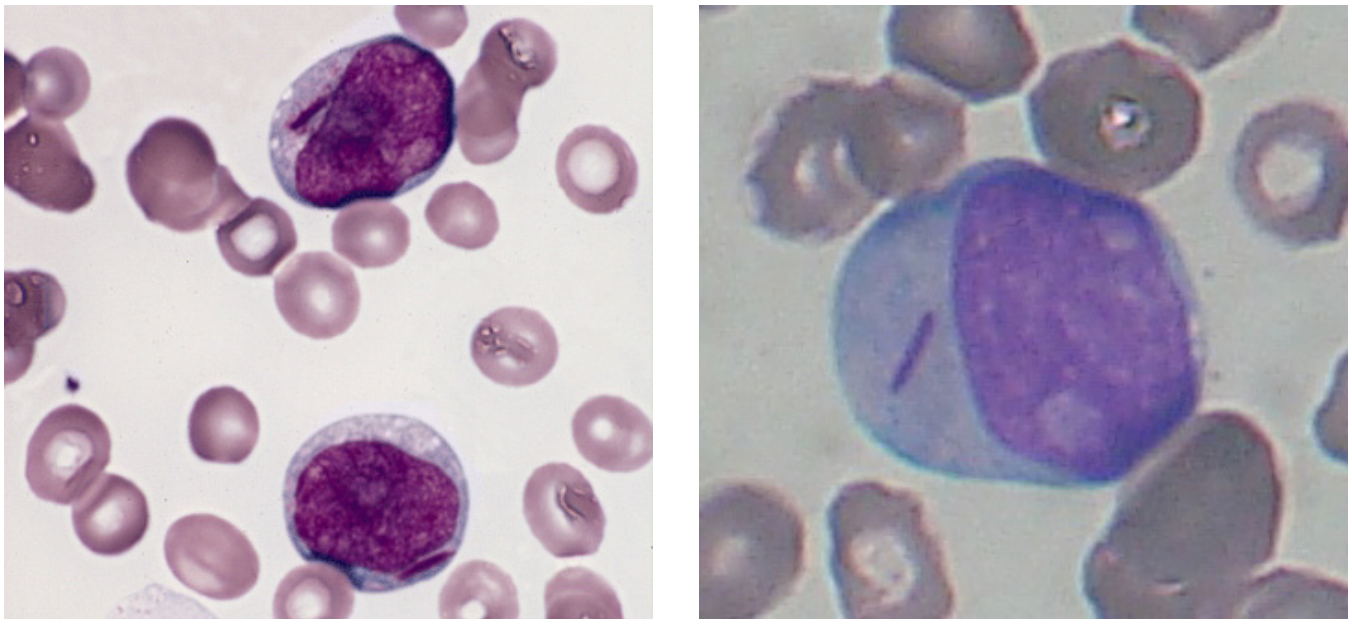
Acute Myelogenous Leukemia

There are four categories of AML according to the WHO, and 7 according to hematopoietic maturation. We want you to see AML as either **translocation-induced** or **CML-induced**; that is, only two AMLs. Those that are translation-induced have a much better prognosis.

If CML progresses to AML through a blast crisis, the patient's cells have undergone such genetic damage in the now-dominant cancer cells that there is little hope of return. There is a translocation in CML, t(9;22), but many more mutations that induce a blast crisis. The accumulation of excess mutations makes it harder to treat.

Previously, the only AML that mattered was the M3 variant, now called **acute promyeloblastic leukemia** (APL). It was the only AML that mattered because it could be treated with **all-trans retinoic acid**. It is caused by a translocation of chromosomes 15 and 17. That translocation—**t(15;17)**—results in a fusion protein that prohibits maturation of the cell. The retinoic acid receptor is necessary to promote differentiation of the blast. By giving these patients extra retinoic acid, differentiation can be induced, and the severity of AML symptoms abated. Now, the only AML that matters is APL, caused by t(15;17). This may seem like an odd statement to someone who has not previously studied leukemia—it sounds like we said the same thing twice. But for those who remember M1–M7 . . . no more memorizing those details, no more trying to visually identify how differentiated a blast is under a microscope. For your studying we want you to see there is the treatable, curable, favorable AML called APL with t(15;17), or there is untreatable, soon-to-be-fatal AML caused by CML.

The presence of **Auer rods** on a blood smear clinches the diagnosis. If you are ever shown a blood smear and have a cell with a lot of cytoplasm, look for the Auer rod. Auer rods are **myeloperoxidase.** The more of them there are, the more likely they are to activate the clotting cascade. There the classic presentation of APL (which tends to have the most Auer rods of any subtype) is **disseminated intravascular coagulation**.



(a) (b)

Figure 3.5: Acute Myelogenous Leukemia
(a) A blood smear of AML. Both cells exhibit an Auer rod. (b) A close up of a cell with APL showing the Auer rod in detail.

Acute myeloid leukemia could be any of the myeloid cell lines. A megakaryoblastic leukemia would make megakaryocytes, not have granules, and not have Auer rods or MPO. Acute monocytic leukemia would make monocytes, and infiltrate the gums. None of these has been bolded. This paragraph is included for completeness. Stick with "*APL t(15;17) and CML to AML t(9;22)*."

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia is caused by the **Philadelphia chromosome**, a translocation between chromosome 9 and 22—**t(9;22)—**which generates the fusion gene **BCR-ABL**. BCR normally has functions that you don't need to know about. What the fusion gene does is cause the BCR gene to act as though it is a receptor tyrosine kinase, though the BCR-ABL fusion protein is in the **cytoplasm**. However, two **BCR monomers dimerize** just like the receptor portion of a receptor tyrosine kinase does. When healthy RTKs dimerize, they autophosphorylate, which turns on kinase activity on the cytoplasmic side, and they phosphorylate cytoplasmic proteins. BCR dimerization in the cytoplasm results in autophosphorylation and subsequent **tyrosine kinase activation**. ABL is normally a kinase. ABL normally has very low levels of constitutive activity. When ABL is attached to BCR, as in BCR-ABL, because BCR dimerizes and autophosphorylates, it is effectively phosphorylating ABL. Phosphorylating ABL **increases its kinase activity**.

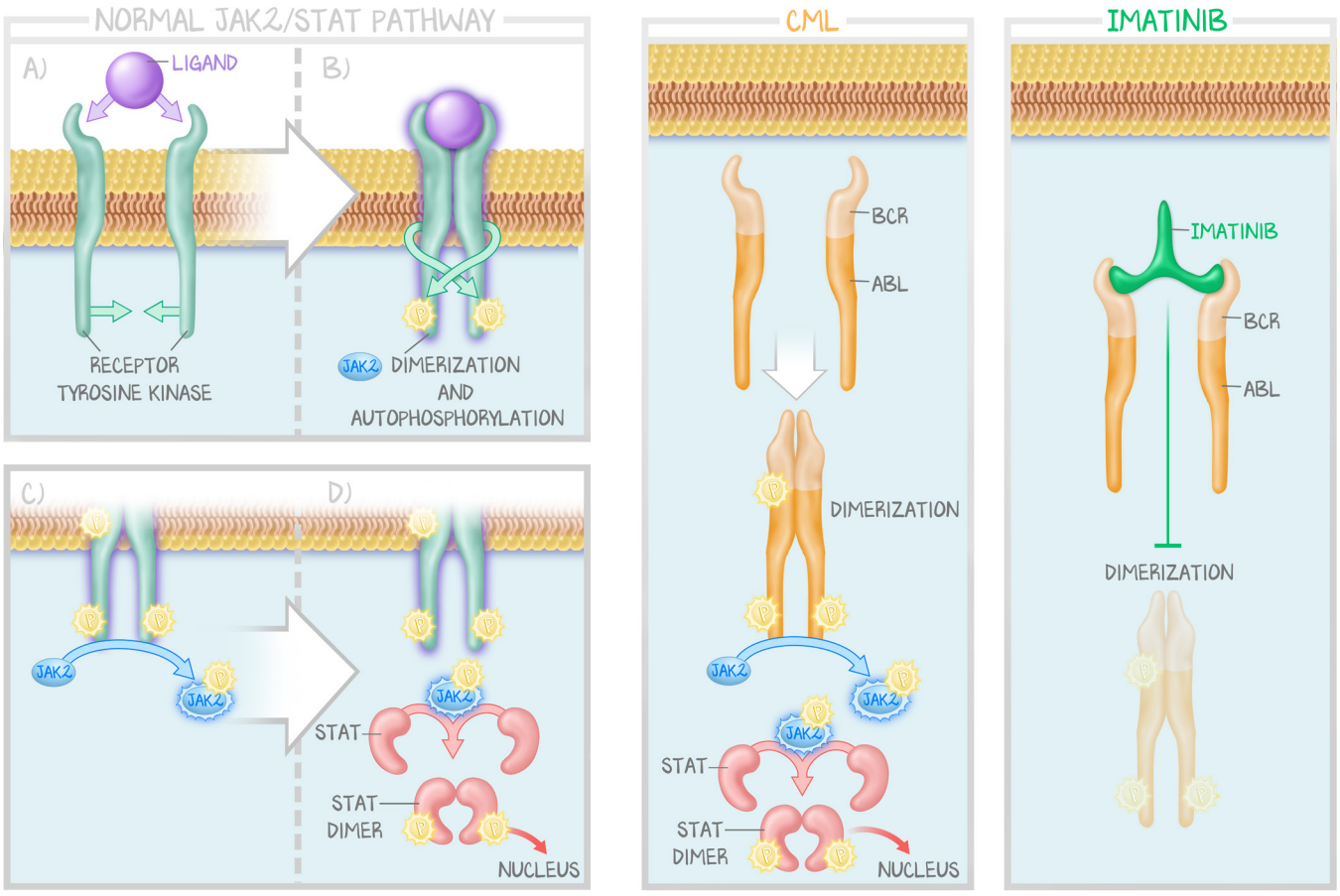
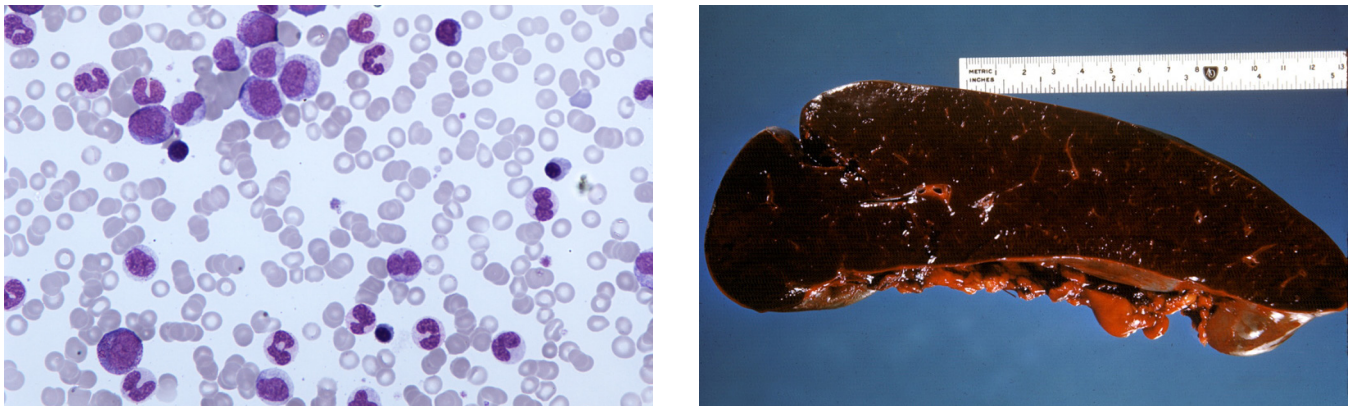


Figure 3.6: Chronic Myelogenous Leukemia
Depiction of the mechanisms and treatment of the BCR-ABL fusion protein.

So you can think of BCR as the "receptor" and ABL as the "kinase." The only problem is that the BCR "receptor" has no ligand, and autoassociates, and so is completely unregulated. It doesn't have an endogenous agonist or antagonist. And it causes cancer. But because BCR-ABL acts like a receptor and needs to dimerize to turn on ABL, we could synthesize an antagonist. And because the BCR-ABL fusion protein exists nowhere except cancer cells, we could inhibit only the BCR-ABL dimerization, leaving all cells that express BCR or ABL separately unaffected. **Imatinib** was the first targeted chemotherapeutic agent, the first to target a cancerous protein. Mutations managed to escape imatinib by mutating the BCR gene slightly. More recent generations (**dasatinib)** are showing immense progress. By inhibiting the proliferation signal, proliferation doesn't proceed. If proliferation doesn't proceed, new mutations cannot be generated. If new mutations cannot be generated, a blast crisis cannot occur. These drugs don't cure the CML, but they prevent its symptoms and progression, which is just about as good as a cure.



(a) (b)

Figure 3.7: CML
(a) CML on a blood smear. Many of the cells are fully matured and those that are not are more towards differentiation. This slide represents the blast crisis. (b) Splenomegaly from increased hematopoiesis.

The disease presents in the fifth and sixth decades of life. As part of our organizer, think, "*CML, age 47*."

The syndrome is characterized by three phases—stable, accelerated, and blast crisis. In the **stable** phase, there is **less than 10% blasts** in the marrow. This phase has an insidious onset. The marrow is crowded, but crowded by mature-appearing cells. The patient may have nonspecific symptoms reflective of **anemia**. The fatigue prompts a CBC that reveals an **extremely elevated WBC count** with a **neutrophilic predominance**. A bone marrow biopsy confirms. Without treatment, median survival is three years, about the same amount of time it takes to progress through the remaining stages. If not treated, the stable phase transitions into the **accelerated phase**. In the accelerated phase there is **rapidly progressive splenomegaly** and **expansion of the cancer** in the marrow, increasing to 10–20% blasts. The cancer has become dedifferentiated and the blasts are taking over. Six to twelve months from the start of the accelerated phase comes the **blast crisis**, with rapid transition to acute leukemia and death.

"Less than 20% blasts" was seen somewhere in this lesson, wasn't it? Yep. When the bone marrow skips CML and is diagnosed as AML, a diagnosis of leukemia requires ≥ 20% blasts, and any less than that is called myelodysplasia. The same bone marrow criterion defines the accelerated phase of CML.

Destiny of CML

All blast crises will result in acute leukemia. It makes sense that a myeloproliferative disorder would result in a myelogenous leukemia. And 70% of the time CML does becomes AML. But some CML can ALSO result in lymphocytic leukemia, as it does 30% of the time. It all comes down to how dedifferentiated the progenitor becomes, or starts off as.

If the malignant transformation occurs at the level of the blast (Figure 3.8), then only one cell line will be produced and dedifferentiation goes back up "one tier," which could explain how we get PV (RBCs predominate) or ET (platelets predominate), but this transformation will also beget some proliferation of the other cell lines. If the malignant transformation occurs at the level of the common myeloid progenitor, then all of its cell lines may increase and dedifferentiation goes back up only "one tier." Going "up one tier" from the common progenitor results in the cancer being a hematopoietic stem cell, which can divide and differentiate into either the myeloid or lymphoid progenitor. If the dedifferentiated tumor then undergoes blast crisis, where it switches from chronic to acute, that HSC-like malignant cell can become either AML or ALL.

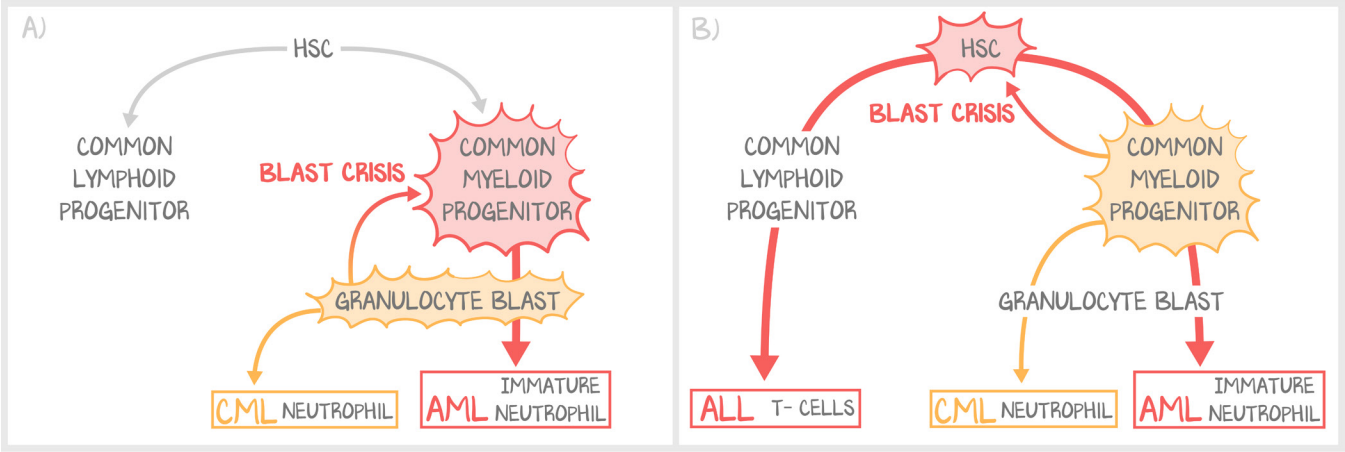


Figure 3.8: One Tier Up
(a) When the original malignancy is in a granulocyte blast, it makes mature neutrphophils, making CML. When there is a blast crisis, the cell dedifferentiates one tier up to a common myeloid progenitor. That cell can make only myeloid lineage, so the blast crisis becomes AML, CML to AML. (b) if the original cancer was in the common myeloid progenitor stage, then it can make neutrophils, thus CML. If it undergoes a blast crisis it goes on tier up becoming an hematopoietic stem cell, which can become either lymphoid or myeloid, generating ALL or AML. Three options, ALL, AML, and AML. 33% of the time CML becomes ALL; 66% of the time CML becomes AML.

Acute Lymphocytic leukemia

ALL is the **most common cancer in childhood**. In our organizer, "ALL is age 7." All ALLs express **TdT**, terminal deoxynucleotidyl transferase, a DNA polymerase that is expressed only in the lymphoblast stage. Mature lymphocytes do not express it, and no cell of the myeloid lineage expresses it. Both B-cell ALL and T-cell ALL lymphoblasts express TdT. Another marker, CD10, also called cALLA, is expressed only by the most immature B-cell lymphoblasts and not by T-cell lymphoblasts.

ALL presents just like AML, an acute leukemia with pancytopenia, anemia, bleeding, infection, bone pain, and fever. The pediatric form of ALL, the kind with an **excellent prognosis**, is the ALL that is caused by a translocation between chromosomes 12 and 21—**t(12:21)**. ALL requires **intrathecal chemotherapy prophylaxis**.

The other form of ALL is the form you get through progression of CML. It is associated with t(9;22) and a dismal prognosis. That is because the t(9;22) allows for the accumulation of many mutations before resulting in blast crisis, where as the sporadic childhood form results from once cell getting one mutation that leads to malignancy. The absence of the accumulation of many mutations first makes for a more treatable cancer.

270+ T-Cell Acute Lymphocytic Lymphoma

Thymic masses in Teenagers are likely to be T-ALL. The T-cell leukemia accumulates in the thymus, and so is not in the blood, and so is actually a lymphoma. When you hear "ALL," the person is likely referring to "B-cell ALL."

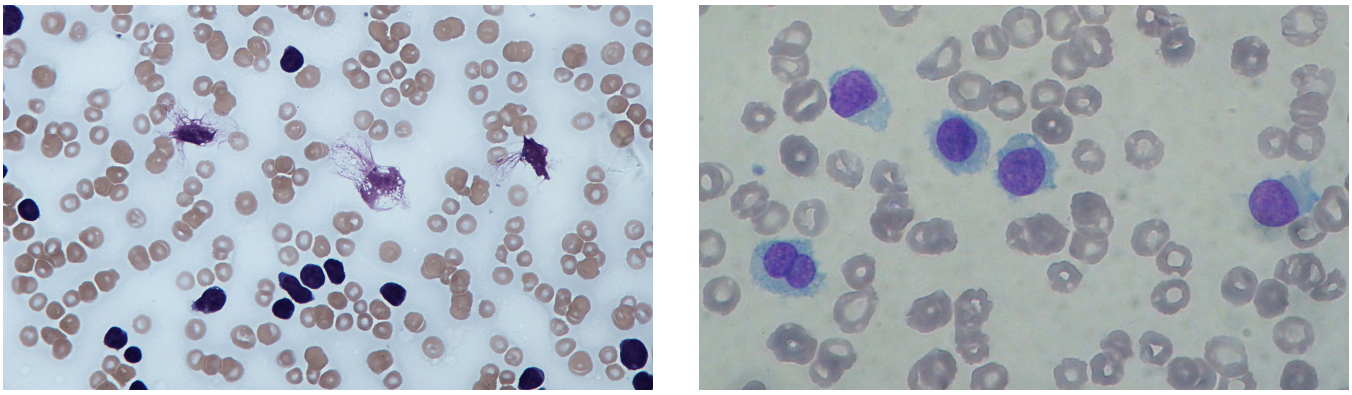
Chronic Lymphocytic Leukemia

This is a condition that affects the elderly. In our organizer, to emphasize that this fact, we say, "CLL is age 87." The patients have very high white counts, usually over 100, with a 99% lymphocyte differential. A blood smear will reveal **smudge cells**, an artifact of preparation of the slide. These cancer cells try to do what their nonmalignant counterparts do—secrete immunoglobulin. They fail. There is an agammaglobulinemia because they don't know how to make IgAnything. When they do, they make bad immunoglobulins that induce autoimmune hemolytic anemia. The typical treatment is to **watch and wait**. As long as the patient remains asymptomatic, do not intervene.

Because mature lymphocytes go to lymph nodes, it is possible that the cancer migrates to a node, then begins proliferating in the node. When that happens, it is a growth of lymphocytes in a focal location, a lymph-oma. Small cell lymphoma is chronic lymphocytic leukemia that has hopped out of the blood and into a node.

CLL can progress, though this is not common. But unlike CML, which can become ALL or AML, CLL transforms not into AML or ALL, but rather into **diffuse large B-cell lymphoma**. Technically, that would be CLL transforming into SLL, which transforms into DLBCL. It should not be surprising to hear that follicular lymphoma, which can progress to DLBCL, is $CD5^+$, and SLL, which can progress to DLBCL, is $CD5^+$. CD5 is a T-cell marker, and yet the two lymphomas that can progress to diffuse large B-cell lymphoma both have $CD5^+$.

A sign of a Richter transformation, the progression of SLL to DLBCL, is a **rapidly enlarging lymph node or spleen**, the indolent SLL now replaced by a more aggressive DLBCL.



(a) (b)

Figure 3.9: Chronic Leukemias
(a) Smudge cell of CLL. They appear smooshed, an artifact of the slide preparation (b) Hair cells of Hairy Cell Leukemia.

270+ Hairy Cell Leukemia

Hairy cell leukemia is so called because a blood smear will reveal leukocytes with slender projections of cytoplasm that look like hair. It causes **marrow fibrosis** and **pancytopenia** and NOT an elevated white count. While flow cytometry is superior to the TRAP test, board examinations still provide the information regarding the TRAP test. Hairy cell leukemia is **TRAP positive**. With loss of bone marrow, extramedullary hematopoiesis initiates in the spleen and the liver. **Splenomegaly** is secondary to physiologic expansion of the red pulp, not from invasion of the cancer. Likewise, hairy cell leukemia does not enter the lymph node.

Hairy cell leukemia responds well to cladribine, an **adenosine deaminase inhibitor**.